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Research Article

Comparative analysis of eight brands of sulfadoxine-pyrimethamine tablets

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Abstract

Purpose: *The aim of the present study is to investigate the physicochemical equivalence of eight brands of tablets containing sulfadoxine-pyrimethamine (antimalarial drug combination) sourced from different retail Pharmacy outlets in the Nigerian market.*

Method: *The quality and physicochemical equivalence of eight different brands of sulfadoxine-pyrimethamine combination tablets were assessed. The assessment included the evaluation of uniformity of weight, friability, crushing strength, disintegration and dissolution tests as well as chemical assay of the tablets.*

Results: *All the eight brands of the tablets passed the British Pharmacopoeia (BP) standards for uniformity of weight, disintegration and crushing strength. Three of the eight brands failed the friability test. One of the brands did not comply with the standard assay of content of active ingredients while another brand did not comply with the USP specifications for dissolution test for sulfadoxine-pyrimethamine tablets. There were no significant differences in the amounts of pyrimethamine and sulfadoxine released from the different brands ($P>0.05$).*

Conclusion: *Only three brands (registered by NAFDAC) out of the eight brands of sulfadoxine-pyrimethamine tablets that were analysed passed all the BP quality specifications and were physically and chemically equivalent. This study highlights the need for constant market monitoring of new products to ascertain their equivalency to the innovator product.*

Keywords: *Chemical equivalence, comparative study, pyrimethamine-sulfadoxine tablets*

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Introduction

The increase in the number of generic drug products from multiple sources has placed people involved in the delivery of health care in a position of having to select one from among several seemingly equivalent products. For instance, in 1975 approximately 9% of all prescription drugs dispensed in the United States were generic versions[1]. This figure rose to 20% in 1984 and 40% in 1991[2]. Over 80% of the approximately 10,000 prescription drugs available in 1990 were obtained from more than one source and variable clinical responses to these dosage forms supplied by two or more drug manufacturers is documented[2]. These variable responses may be due to formulation ingredients employed, methods of handling, packaging and storage and even the rigors of in-process quality control. Thus, there is need to determine their pharmaceutical and therapeutic equivalence in order to ensure interchangeability.

However, many developing countries do not have an effective means of monitoring the quality of generic drug products in the market. This results in widespread distribution of substandard and/or counterfeit drug products. It was in view of this fact that the World Health Organization issued guidelines for global standard and requirements for the registration, assessment, marketing, authorization and quality control of generic pharmaceutical products[3]. This was to give technical guidelines to national regulatory authorities such as NAFDAC (National Agency for Food, Drug, Administration and Control), which is responsible for drug administration and control in Nigeria, on the quality of drug dosage forms generally available in the market. Generic drug products must satisfy the same standards of quality, efficacy and safety as those applicable to the innovator products. Preliminary physicochemical assessment of the products is very important and *in vitro* dissolution testing can be a valuable predictor of the *in vivo* bioavailability and bioequivalence of oral solid dosage forms[4].

Sulfadoxine-pyrimethamine (500 mg and 25 mg, respectively) combination tablets are commonly used for the prophylaxis and suppression of chloroquine-resistant *Plasmodium falciparum* malaria, which is a cause of high mortality among children in tropical Africa. The action of the sulfadoxine component is due to its effect in potentiating the effect of pyrimethamine. This action is presumably due to sequential blockade of different stages in plasmodial synthesis of nucleotides[5]. Apart from Fansidar® (Roche Pharmaceuticals, Lagos), which is an expensive innovator product, several generic antimalarials are marketed in Nigeria that are generally less expensive. Hence there is the need to assess the bioequivalence of these generic products with the innovator product.

Thus, in the present study the equivalence of eight brands (including the innovator product) of sulfadoxine-pyrimethamine tablets sourced from retail pharmacies in Ibadan, Nigeria was determined using *in vitro* methods. This preliminary study is aimed at obtaining baseline data towards the establishment of bioequivalence of the tablets.

Experimental

Materials

Eight brands of Sulfadoxine-pyrimethamine tablets (A to H) were obtained from different retail outlets in Nigeria. The manufacture and expiry dates are shown in Table 1.

Physical Measurements

Twenty tablets selected at random were weighed individually and their average weight calculated to determine the weight uniformity[6]. The percentage deviation of each tablet from the average weight was determined. Twenty tablets were caused to cascade in a friabilator (Erweka TA,

Table 1: Country of origin, manufacture and expiry dates of eight brands of sulfadoxine-pyrimethamine tablets

Brand	Date of Manufacture	Expiry Date	Country of Origin	NAFDAC* Registration
A	March, 2000	March, 2005	Nigeria	Yes
B	June, 1999	June, 2003	United Kingdom	Yes
C	January, 2000	August, 2002	India	No
D	February, 2000	January, 2004	India	No
E	January, 1999	December, 2002	India	Yes
F	February, 1999	January, 2003	India	Yes
G	March, 2000	December, 2003	India	No
H	January, 2000	December, 2003	India	No

**National Agency for Food and Drugs Administration and Control, Abuja, Nigeria*

Germany) rotated at 25 rpm for 4 min. The weight loss was determined as a percentage of the initial weight.

Crushing strength of each of 9 tablets per brand was determined using the PTB 301 hardness tester (Pharmatest, Switzerland). The load required to break the tablets into two halves was determined.

The disintegration times of six tablets per brand were determined in distilled water at 37 ± 0.5 ^{o}C using the Apex Tablet Disintegration Apparatus (Apex Construction Ltd., Kent, U.K). Determinations were done in triplicate.

Dissolution tests on the tablets were carried out using the Hanson Easy Lift Dissolution Station Apparatus (Hanson Research laboratories, London, U.K) fitted with a basket rotated at 75 rpm[6]. The buffer (500 ml), pH 6.8, was poured into the vessel maintained at 37±0.5 ^{o}C. One tablet of each brand was placed in the basket and lowered into the vessel containing the dissolution medium. Samples (5 ml) were withdrawn at timed intervals and replaced with fresh dissolution medium. The samples were filtered and diluted appropriately with the buffer solution and the absorbance of the solution was measured at 220 nm for sulfadoxine and 288 nm for pyrimethamine. The regression equation for the calibration curves prepared for each drug component in phosphate buffer pH 6.8 was $y = 0.016x + 0.007$, $r^2 = 0.99$; and $y = 0.200x + 0.002$, $r^2 = 0.99$ for pyrimethamine and sulfadoxine, respectively.

The graph of the amount of sulfadoxine and pyrimethamine dissolved versus time were plotted from which T_{50} and T_{70} (the time required for 50% and 70% of the active drug to be dissolved respectively) and amount dissolved at 30 min were obtained for each brand. Determinations were done in triplicate.

Assay of Active ingredient

Pyrimethamine: Twenty tablets were weighed and powdered. Hot 0.1 M HCl (25 ml) was added to 225 mg of powder containing 12.5 mg pyrimethamine. This was heated on a water bath for 30 min, with occasional swirling. It was then placed in an ultrasonic bath for 30 min, removed and cooled to room temperature. Sufficient quantity of 0.1 M HCl was added to produce 50 ml. The solution was filtered and 2.5 ml of the filtrate was diluted with 0.1 M HCl to produce 50 ml. The amount of pyrimethamine was determined at 288 nm using a Lambda 3B UV-visible spectro-photometer (Perkin-Elmer, USA).

Table 2: Physicochemical properties of eight brands of sulfadoxine-pyrimethamine tablets

Parameter	Weight uniformity Test, mg (mean ± sd)	Friability, % loss (mean ± sd)	Crushing strength, KgF (mean ± sd)	Disintegration time, min (mean ± sd)
Brand A	538.8±9.2	0.2±0.01	15.7±1.7	1.8±1.0
Brand B	527.4±1.0	0.1± 0.1	11.2±0.8	8.3±1.2
Brand C	526.5±30.9	1.2 ± 0.2*	14.3±2.3	4.4±0.5
Brand D	525.7±17.9	0.4 ±0.1	15.3±0.4	2.2±0.9
Brand E	525.7±17.4	1.5± 0.1*	7.8±1.6	2.5±1.0
Brand F	527.3±15.7	0.7±0.1	13.7±3.0	2.0±0.8
Brand G	526.1±17.5	0.5 ± 0.1	12.1±3.1	3.1±1.4
Brand H	521.7±13.6	1.2 ± 0.2*	12.5±0.8	2.5±0.1

**Failed to meet BP specifications*

Sulfadoxine: The amount of sulfadoxine present in tablet was assayed using the BP 1998 method. Twenty tablets were dissolved in 50 ml of 2 M HCl and 3 g of potassium bromide was added. The resulting solution was cooled in iced water and titrated slowly, adding 0.1 M sodium nitrite VS with constant stirring. The end point was determined using starch iodide paper[6]. Sodium nitrite (1 ml of 0.1 M) is equivalent to 29.24 mg $C_{12}H_{14}N_4O_4S$.

Data Analysis

Data for weight uniformity test, friability, crushing strength and the disintegration and dissolution times of the tablets were analysed by determining the mean ± standard deviation.

Statistical analysis: The statistical significance difference in the amount of sulfadoxine and pyrimethamine released from each brand compared with the innovator product was carried out with Student T-test using Microsoft Excel software. At 95% confidence interval, 2-tailed *p* values less than or equal to 0.05 were considered significant.

Results and Discussion

All the samples used for the study were within their shelf life at the time of investigation. Four out of the eight brands of the sulfadoxine-pyrimethamine tablets have been registered by NAFDAC. The results of the physicochemical properties of the various brands of sulfadoxine-pyrimethamine are presented in Table 2. All brands showed acceptable uniformity of weight as none had percent deviation in weight greater than 5% as stipulated by the British Pharmacopoeia 1998[6]. The significance of this test is to ensure that the tablets in each Lot are within the appropriate size range.

The crushing strength of the tablets is an essential criterion in the determination of the ability of the tablets to resist chipping, abrasion or breakage under conditions of storage, transportation and handling before storage. The results showed that the brands examined had mean crushing strength within the range of 7.8 - 15.68 kgF. Generally, a hardness of 4 kgF is normally considered to be minimum for a satisfactory tablet[7, 9].

Table 3: Content of sulfadoxine and pyrimethamine in the combination tablets

Brand Code	%w/w (mean ± sd)	
	Sulfadoxine	Pyrimethamine
A	102.4 ± 0.1	102.2 ± 1.1
B	102.9 ± 0.1	99.0 ± 0.6
C	103.5 ± 0.1	102.3 ± 1.1
D	101.8 ± 0.1	141.2 ± 2.1*
E	102.4 ± 0.1	99.8 ± 0.6
F	101.2 ± 0.1	103.1 ± 1.2
G	102.5 ± 0.1	92.0 ± 0.0
H	101.3 ± 0.1	105.1 ± 0.1

**Failed to meet BP specifications*

Another tablet property related to crushing strength is friability, which is designed to evaluate the ability of the tablet to withstand abrasion during packaging, handling and shipping. For compressed tablets, percentage loss in weight of less than 1% is usually considered acceptable[9]. The results showed that brands A, B, D, F and G conformed to the required standard for friability, while brands C, E and H failed to comply. This failure could have resulted from the use of inadequate or insufficient amount of binding agent during formulation, inadequate moisture content during compression or insufficient compression pressure during tableting.

The disintegration test measures the time required for tablets to disintegrate into particles. This is a necessary condition for dissolution and could be the rate-determining step in the process of drug absorption. The BP 1998 stipulates a disintegration time of not more 15 min for uncoated tablets. The results of the disintegration test are presented in Table 2. The results showed that all the brands passed the disintegration test.

The results of the assays of chemical content to determine the amount of sulfadoxine and pyrimethamine present in each formulation are presented in Table 3. They showed that all the brands contain between 90% and 110% of the labelled amount specified for sulfadoxine[5]. There was no statistically significant difference between the different brands of the drug and the innovator product, A. Furthermore, all the brands of the tablets except brand D passed the test for the content of pyrimethamine. The pyrimethamine content of brand D was 141.2% which was significantly different from the innovator product, A ($p < 0.05$). This could be due to poor preparation techniques during formulation and subsequent manufacturing. An important character of powders during mixing is segregation, which occurs due to differences in particle size. Furthermore, the amount of pyrimethamine in the combination tablet is relatively small (i.e. 25 mg), which means any demixing or segregation during processing will result in non-uniformity of content.

The dissolution test is a measure of the amount of the drug released into the dissolution medium with time. The United States Pharmacopoeia stipulates that at 30 min, all tablets should have released into the dissolution medium an amount not less than 60% of the labelled amount of sulfadoxine and pyrimethamine. The dissolution profiles of pyrimethamine and sulfadoxine in all brands are presented in Figures 1 and 2, respectively. The time for 50% and 70% (T_{50} and T_{70}, respectively) of drug to be released and the amount of drug released at 30 min are presented in Table 4. All the brands passed the dissolution test except brand G which showed only 58.6% and 52.8% of sulfadoxine and pyrimethamine released, respectively at 30 min. This may be due to the nature of excipients used or the formulation process. It has been shown by Abdou[10] that the dissolution rate of a pure drug can be altered significantly when mixed with various adjuncts during the manufacturing process of solid dosage forms. Furthermore, the fast disintegrating

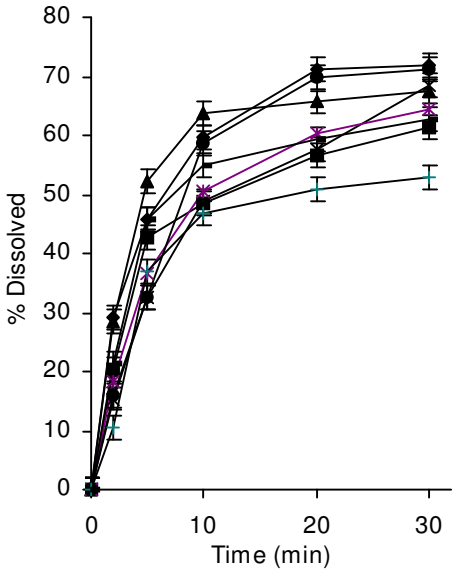

Figure 1: Dissolution profiles of pyrimethamine from eight different brands of sulfadoxine-pyrimethamine tablets in phosphate buffer pH 6.8

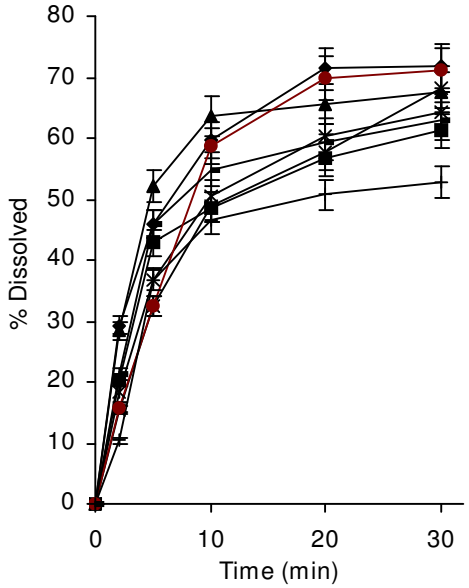

Figure 2: Dissolution profiles of sulfadoxine from eight different brands of sulfadoxine-pyrimethamine tablets in phosphate buffer pH 6.8

characteristics of Brand G is not reflected in the dissolution profile. This could be due to the fact that the disintegrated particles though small enough to pass through the screen of the dissolution basket, may have retained the active drug within their hard cores and hence did not release the drug into the dissolution medium. This implies that the product may not release a significant amount of the drug on absorption into the systemic circulation and thus leading to therapeutic failure.

Table 4: Dissolution parameters of the eight brands of sulfadoxine-pyrimethamine tablets (mean ± sd)

	T_{50} (min)		T_{70} (min)		% Dissolved at 30 min	
Product	Sulfadoxine	Pyrimethamine	Sulfadoxine	Pyrimethamine	Sulfadoxine	Pyrimethamine
A	4.8 ± 0.2	6.0 ± 2.2	10.0 ± 2.1	18.0 ± 3.1	88.7 ± 1.4	71.8 ± 2.8
B	6.0 ± 1.2	12.0 ± 0.3	29.5 ± 1.3	62.4 ± 1.7	70.6 ± 2.1	61.3 ± 0.8
C	5.4 ± 0.1	4.9 ± 2.4	29.3 ± 0.5	68.2 ± 1.8	72.6 ± 1.6	67.4 ± 1.5
D	9.8 ± 3.1	12.0 ± 1.2	65.0 ± 2.4	68.0 ± 0.4	63.3 ± 1.1	68.3 ± 3.2
E	5.5 ± 2.3	10.0 ± 3.2	68.2 ± 2.1	66.0 ± 0.5	64.4 ± 0.3	64.4 ± 1.5
F	7.0 ± 2.3	8.0 ± 2.1	30.0 ± 2.4	20.0 ± 2.9	71.9 ± 2.8	71.2 ± 4.1
G	9.8 ± 3.5	18.0 ± 1.5	58.5 ± 3.4	52.0 ± 1.4	58.6 ± 0.7	52.8 ± 1.7*
H	7.0 ± 2.1	6.0 ± 0.2	64.0 ±1.6	64.0 ± 2.2	63.1 ± 2.4	62.8 ± 2.9

** Failed to meet USP specification*

Conclusion

Only three brands (registered by NAFDAC) out of the eight brands of sulfadoxine-pyrimethamine tablets analysed passed all the BP quality specifications and were physically and chemically equivalent. These three brands can be substituted for each other in their prescription and use.

This study highlights the problems associated with a multi-component dosage form especially one like the sulfadoxine-pyrimethamine combination where the efficacy of the formulation depends on the precise amount of the active ingredients being present and released.

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